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Role of the Radionuclide Metrology in Nuclear Medicine

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1. Introduction

Nuclear medicine practices rely on the use of radiopharmaceuticals, for diagnosis and therapy purposes. Their use is based on the incorporation in the human body through a medical procedure: intravenous injection, ingestion, or inhalation. The quality of the administration procedure is tightly influenced by the following determining factors: the administration of the right activity to the patient, such as prescribed by the medical doctor, and the quality of the radiopharmaceutical product. The full control of these parameters is obtained by using high quality measurement equipment and following well established procedures for the measurement and application of the radiopharmaceutical.

The radiopharmacy units, the measurement equipment providers and the nuclear medicine units can fulfill these requirements only by using calibrated instrumentation and following validated measurement methods. The technical support is offered by the Radionuclide Metrology Laboratories (RML) which can assure the continuity of the metrological traceability chain of measurement up to the highest, primary radioactivity standards. The metrological traceability and its chain are defined by the document: *"BIPM, JCGM 200:2008 – International vocabulary of metrology – Basic and general concepts and associated terms (VIM)"*, as:

- *"Metrological traceability – property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty"*
- *"Metrological traceability chain – sequence of measurement standards and calibrations that is used to relate a measurement result to a reference"*

From these definitions one can deduce the role of the RMLs: to develop activity standards, to validate them in relation with the International System of Units (SI) and to disseminate them as radioactive standard sources and solutions, or calibration services to the implied entities.

This chapter of the book presents the following aspects:

- Measurement requirements in radiopharmacy, in measurement instrument calibration process, and in nuclear medicine units;
- Role of the Radionuclide Metrology Laboratory in the practical accomplishment of these requirements

2. Radiopharmaceutical products and their characterization by measurements

2.1 Types of radiopharmaceutical products

A radipharmaceutical (RPM) product contains a radionuclide in an adequate chemical form, the transporter, which conducts it towards the organ or tissue of interest, when it is administrated to the patient "in vivo" by ingestion, inhalation or intravenous injection. In the case of diagnosis the radionuclide is used as a "tracer", while in therapy it is employed due to the cytotoxic effect of the emitted ionizing radiations. The radiopharmaceuticals are presented as ingerable gelatin capsules (or solutions), injectable solutions and inhalation gases.

2.1.1 Transporters

Various types of transporters are used, formulated such as to assure a maximum localization of the radiopharmaceutical in the zone of interest while exposing the neibouring area to minimum detriment (Kornyei.2008, Mikolajczak. 2008). The types of transporters are generally similar for both of nuclear medicine procedures, diagnosis and therapy; some formulations are presented as follows:

- Simple inorganic compounds such as salts, containing the radionuclide in an ionic form: $Na^{99m}TcO_4$, ^{131}INa, $^{89}SrCl_2$, $Na^{186,188}ReO_4$
- Simple gas molecules: $^{11}CO_2$, $^{15}O_2$, ^{81m}Kr
- Labeled organic molecules: ^{18}F-DG; ^{67}Ga-cytrate
- Metal-ligand complexes: ^{99m}Tc-MDP, DTPA; ^{188}Re-HEDP; ^{177}Lu-EDTMP
- Colloids, labeled micro and nano spheres: ^{99m}Tc-fytate
- Labeled biomolecules:
  i. Monoclonal antibodies (mAb): ^{90}Y-anti-CD20; ^{188}Re-anti-VEGF
  ii. Meta Iodo Benzil Guanidine (MIBG)-^{131}I
  iii. Peptide Receptor Radionuclide, somatostatin analogous: Pentetroid-DTPA-^{111}In, TOC-HYNIC-^{99m}Tc. ^{188}Re-DOTA-Lan and ^{188}Re-Lan.

The detailed description of these compounds is outside the scope of the chapter.

2.1.2 Radionuclides

In contrast with the transport molecules, the choice of the radionuclides differs for the two types of nuclear medicine procedures: diagnosis and therapy.

Radionuclide diagnosis principle: The incorporated radiopharmaceutical product, localized at the interest zone emits gamma-rays, which cross the body and are detected by the gamma cameras, containing a detection system, based on the use of scintillation detectors and a network of photomultipliers. A bi-dimensional image, called scintigram, is obtained; if the computer tomography principle is applied, a 3D image appears. In principle it is necessary to use as much as possible of the emitted radiation for detection and to avoid the unnecessary irradiation of the body; the irradiation detriment is expressed in terms of committed effective dose per activity unit, *E/A*. For this reason, the choice of radionuclides is focussed on the use of radionuclides with short half life and emitting low energy and intensity electrons and abundant gamma-rays, not much absorbed inside the body, and situated in the optimal energy detection interval, 100 – 600 keV. Two types of diagnosis procedures are in use:

- Single Photon Emission Tomography (SPET) is based on the use of a single detector and of radionuclides decaying by isomeric transition, such as ^{99m}Tc, and by electron capture, ^{123}I. As an exception, ^{131}I emitting beta-gamma radiations, is still used in some special procedures, like the iodine uptake in thyroidal investigations.

- Positron Emission Tomography (PET), sometimes associated with *x*-ray tomography, PET/CT. In this case, radionuclides decaying by positron emission are used. The stopped, or in flight, positron annihilates with a neighbouring electron, and two 511 keV annihilation quanta at an angle of 180^0 are emitted. These quanta can be detected in coincidence, using two detectors situated at 180^0. The procedure allows a much better resolution and consequently a more precise diagnosis, due to the measurement of coincident radiations. The positron emitters used for PET systems have short half life and for this reason the *E/A* value is low, although they emit positive electrons, absorbed inside the body. The most used radionuclide is ^{18}F.

Table 1 presents a list of radionuclides used for the production of radiopharmaceuticals, in terms of production mode, nuclear decay data and *E/A*. Referring the *E/A* value, it is strongly dependent on the type of radiopharmaceutical, diagnostic procedure and the age of the patient; only for a rough information, the comparative dose values due to the ingestion of radionuclides by the adult public (ICRP 1996c) are given, in order to emphasize the strong dependence of the dose on the characteristics of the nuclear decay scheme.

The values of *E/A* from Table 1 are based on the Medical Internal Radiation Dose (MIRD) model, while at present time the calculation models use the "voxel phantom", defined in international documents as *"a computational anthropomorphic phantom based on medical tomographic images where the anatomy is described by small three dimensional volume elements (voxels) specifying the density and the atomic composition of the various organs and tissues of the human body"*. A special attention is paid to the radionuclide ^{99m}Tc, used nowadays in about 80% of the world diagnosis procedures. Its widespread use is due to several properties:

i. Its committed effective dose of activity unit is *E/A* =0.022mSv/MBq and the corresponding doses in the diagnostic procedures are generally within the limits (1 -2) mSv, due to the short half-life and to the small content of low energy electrons.
ii. The 140.5 keV quanta are emitted with a high intensity, being situated near the maximum detection efficiency of the usual scintillators.
iii. It can be extracted from a ^{99}Mo generator (2.75 d,) a reasonable life time for transport and use for a period of two weeks, or can be prepared in a pharmaceutical unit and delivered to the neighboring hospitals in the same day.
iv. It is carrier free and due to its position in the Mendeleev Table, the VII-b group, with 7 valence electrons, it can be used for binding in various chemical compounds, with various valence states.

Radionuclide (targeted) therapy principle. The incorporated radiopharmaceutical is localized in the biological formation to be destroyed by irradiation. In this case, the entire energy of particles must be transferred to the matter. Consequently, low range radiations, such as: alpha particles and electrons - beta radiation, Auger and conversion electrons, are useful. This is the reason for which alpha, strong beta with high energy, electron capture and conversion decaying radionuclides are used. Lately a special attention is given to the beta-gamma triangular decay scheme radionuclides, with strong beta and weak gamma – ray energies and intensities, due to the ability to be monitored by a gamma camera during the treatment procedure. The half life can be from hours up to tens of days, in order to assure the prescribed dose to the biological formation to be destroyed. The choice of the radionuclides takes into account their chemical properties, as well as their radiations range in the tissue, which must be comparable with the dimensions of the biological formation to be destroyed. Table 2 presents a list of therapeutical radionuclides, with their modes of production, nuclear decay parameters and the tissue range.

Type of Diagnostic	Radio nuclide	Obtaining	Half life	Emitted radiations			*E/A*, *mSv/MBq* adults, ingestion
				Type	Energy, keV	Intensity %	
SPET	^{131}I	NR*: ^{130}Te (n,γ)^{131}Te, β decay, ^{131}I, or ^{235}U fission	8.02 d	β– γ	248-606 max 364.5	100 81.6	22
	^{123}I	Cyclotrone: ^{123}Te(p,n)^{123}I	13.2 h	e X γ	127-158 27-32 159	3.36 85.6 83.3	0.22
	^{67}Ga	Cyclotrone: ^{67}Zn(p,n)^{67}Ga	3.26 d	e γ	84-93 91 -393	35 87	0.19
	^{201}Tl	Cyclotrone: ^{203}Ta(d,4n)^{201}Pb. E.C.^{201}Tl	3.04 d	e X Y	16-153 12-82 167.5	51.8 140 10	0.095
	^{99m}Tc	NR: ^{99}Mo generator (2.75 d) ^{98}Mo(n, γ)^{99}Mo or ^{235}U fission	6.007 h	e X γ	120-138 18.3-20.7 140.5	11 7.6 89	0.022 / diagnostic 0.005-0.029 (Toohey & Stabin. 1996)
	^{111}In	Cyclotrone: ^{111}Cd(p,n)^{111}In	2.80 d	e X γ	145-219 23-27 171.3 245.4	13.6 3.2 90.6 94	0.29
	^{81m}Kr	Cyclotrone: ^{81}Rb generator (4.25 h) ^{79}Br(α,2n)^{81}Rb	12.8 s	e X γ	176 -188 12.6-14.1 190.3	32.1 16.8 67.1	0.00004 inhallation
PET	^{18}F	Cyclotrone: ^{18}O(p,n)^{18}F; ^{16}O(α,pn)^{18}F; ^{20}Ne(d,α)^{18}F	110 min	β^+ $\gamma^{\pm}$	634 max, tissue range 2mm 511	96.9 194	0.049
	^{11}C	Cyclotrone: ^{14}N(p, α)^{11}C	20.4 min	β^+ $\gamma^{\pm}$	960 max 511	100 200	0.024
	^{68}Ga	^{68}Ge generator (270.83 d) Cyclotrone: ^{66}Zn(α,2n)^{68}Ge	67.7 min	β^+ $\gamma^{\pm}$	1899 max 511	88 178	0.10
	^{64}Cu	NR:^{63}Cu(n,γ)^{64}Cu Cyclotrone: ^{64}Zn(d,2p)^{64}Cu	12.70 h	$\beta^{\pm}$ $\gamma^{\pm}$	653 max 511	56.9 35.7	0.12

NR* = Nuclear Reactor. In the future, most of NR produced radionuclides is expected to be obtained from high neutron flux sources, based on the use of a proton accelerator and the emission of neutrons by the accelerated protons reaction with a mercury target. ^{99}Mo can be produced also at a linear accelerator: $^{100}\mathrm{Mo}(\gamma,n)^{99}\mathrm{Mo}$

Table 1. The most used radionuclides for diagnosis. Monographie BIPM-5 (Bé et al. 2004), ICRP1996c (1996).

Type	Radio nuclide	Obtaining	Half life	Type of radiations	Energy, keV; Intensity	Tissue range Max./Mean
Alpha emitters	^{211}At	Cyclotrone ^{209}Bi (α,2n)^{211}At	7.21 h	α	5868-7448; 100%	80 μm
	^{213}Bi ^{225}Ac (10 d) generator	^{225}Ac is in ^{237}Np decay chain or cyclotrone: ^{226}Ra(p,2n)^{225}Ac	45.6 min	α β	5869; 2% 987-1426; 97%	70 μm 2.5 mm
	^{212}Bi ^{212}Pb (10.64h) generator	^{212}Pb is in natural ^{232}Th chain, or Cyclotrone: ^{210}Po (t, p)^{212}Bi	Bi-212 60.54 min	α β	6050-6090 ; 35.8% 1527-2250 ; 64.2%	80 μm 4.0 mm
Electron capture (EC) radio nuclides	^{125}I	NR: ^{124}Xe (n, γ) ^{125}Xe, EC, ^{125}I	59.90 d	Auger L Auger K	3.7; 79.3% 22.7 - 34.5; 33.9%	Tens of nm about 47μm
	^{117m}Sn	NR: ^{116}Sn(n, γ)^{117m}Sn	13.6d	Internal conversion electrons	127 keV 152 keV	210 μm 290 μm
Pure beta emitters	^{32}P	NR: ^{32}S(n,p)^{32}P	14.28 d	β	Max 1710, mean 695.5; 100%	9.8 mm/ 2.8 mm
	^{90}Y	NR: ^{89}Y(n,γ)^{90}Y; or ^{235}U fission: Generator: ^{90}Sr (28.15 y):	2.67 d	β	Max 2284, mean 939; 100%	12 mm/ 4.0 mm
	^{89}Sr	NR: ^{88}Sr (n,γ)^{89}Sr or ^{235}U fission	50.65 d	β	Max 1492, mean 584; 100%	8 mm/ 2.5 mm
Beta - gamma emitters	^{131}I	NR: ^{130}Te(n, γ)^{131}Te, β decay, ^{131}I or ^{235}U fission	8.023 d	β	Max 338-605, mean 97-192 ; 100%	4mm/ 0.8 mm
	^{153}Sm	NR: ^{152}Sm(n, γ) ^{153}Sm	1.956 d	β	Max 634-807 , mean 200-263 ;100%	5 mm/ 1.2 mm
	^{177}Lu	NR: ^{176}Lu (n, γ)^{177}Lu or: ^{176}Yb(n, γ)^{177}Yb, β decay, ^{177}Lu	6.734 d	β	Max 175.8-497.1, mean 47-149 ;100%	1.6 mm/ 0.7 mm
	^{186}Re**	NR: ^{185}Re(n, γ)^{186}Re	3.775 d	β	Max 939.4-1077, mean 309-362; 93.1%	5.0mm/ 1.7 mm

Type	Radio nuclide	Obtaining	Half life	Type of radiations	Energy, keV; Intensity	Tissue range Max./Mean
	^{188}Re**	NR: ^{187}Re(n, γ)^{188}Re or ^{186}W(n, γ)^{187} W (n, γ)^{188}W (69.4 d) Generator	16.98 h	β	Max 1962-2118. mean 706-784;100%	11 mm/ 3.5 mm

**) When a natural Rhenium target is irradiated, a mixture ^{186}Re+^{188}Re is obtained. It can be used in this composition, for the short time irradiation of the external part of large dimension tumors by ^{188}Re and for the long time irradiation of their cores by ^{186}Re. Otherwise, after a week period ^{188}Re decays and almost pure ^{186}Re is obtained. ^{186}Re and ^{188}Re are very important for the obtaining of therapy pharmaceuticals, due to their similar chemical behavior (VII b group) with ^{99m}Tc, very extensively studied.

Table 2. Radionuclides used for therapy radiopharmaceuticals.

2.2 Technical parameters of radiopharmaceuticals and control methods

One radiopharmaceutical product is characterized by several types of parameters, whose determination requires a very good knowledge of the physico-nuclear parameters of the radionuclide and the use of adequate methods and equipment for measurements. Their accepted limit values and methods of determination are described in international and national technical regulatory documents, such as the European Pharmacopoeia (2002). It is considered that the radiopharmaceuticals are products with a high pharmaceutical risk. The parameters are determined first of all in the radiopharmacy, which must dispose of control laboratories in full compliance with the requirements for Good Laboratory Practice (GLP) and accredited according to the international standard "*General Requirements for the Competence of Testing and Calibration Laboratories*", ISO/IEC 17025:2005. Their determined values are confirmed by the national control laboratories, or are internationally recognized by conventions. Some parameters are controlled only in radiopharmacy, while others are compulsory for the nuclear medicine units, mainly when supplementary operations are carried. A detailed description of the requirements and of their accomplishment mode, regarding quality assurance in radiopharmaceutical measurement is presented in the document *Technical Report Series 454 (TRS 454)*, elaborated by the International Atomic Energy Agency (IAEA) (2006).

Three types of radiopharmaceuticals' parameters are generally defined and controlled: radiometrologic, physico-chemical and biological-microbiological parameters.

2.2.1 Radiometrologic parameters and their determination

(i) Activity, Bq, and derived quantity Radioactive Concentration (Massic Activity), expressed in Bq g^{-1} of solution, or Bq mL^{-1}. These are basic parameters of a radiopharmaceutical product, as the precise determination of the activity administrated to the patient, in full compliance with the prescriptions of the medical doctor, determines his/her committed effective dose, mSv, in radionuclide diagnosis and absorbed dose in the organ/tissue, mGy, in radionuclide therapy, and assures the safety and effectiveness of the medical procedure. Due to this reason, the special requirements regarding the reporting of total activity of a radiopharmaceutical product, on a reference time, are specified by the *Basic Safety Standards*

(*1996), para.II.19,* such as follows: *"the calibration of sources used for medical exposure shall be traceable to a Standard dosimetry laboratory*" and "*unsealed sources for nuclear medicine procedures shall be calibrated in terms of activity of the radiopharmaceutical to be administrated, the activity being determined and recorded at the time of administration*". The conclusion of these assertions is that the activity must be precisely measured and the metrological traceability up to the primary level must be assured.

In radiopharmacy and nuclear medicine units, the activity is usually determined using Radionuclide Activity Calibrators, or Dose Calibrators. They contain a reentrant (well type) ionization chamber under pressure, connected to an electrometric system. The manufacturers perform the calibration of the equipment in terms of calibration factors, introduced in dial settings, established for a list of the most used medical radionuclides. The calibrations are performed using sets of standard solutions, provided by the radionuclide metrology laboratories or by commercial producers, having metrological traceability to a primary activity standard declared. Usually, these factors are determined for various types of recipients used in hospitals, such as: P6 or Schott 10-R vials, syringes, gelatin iodide capsules, etc.

The pharmacopoeias impose the uncertainty limits in the measurement of activity, as: <5% for therapy and <10% for dignosis. The activity is measured in radiopharmacy, but it must be measured also in the hospital, as several operations, such as portioning, administration with a syringe, are carried by the involved staff**.** Due to the crucial importance of these measuremens, the radionuclide calibrator precision in the calibration and maintenance of its corresponding technical condition, together with the correct method of activity measurement in the nuclear medicine units are matters of concern at international level. The IAEA initiated a program aimed to improve and harmonize the quality of activity measurements. In November 2002 a group of consultants had a meeting in the IAEA Vienna headquarters, giving advice on the Methodology of Radioactivity Standardization. The Coordinated Research Project (CRP) codified as: E2.10.05, entitled: *"Harmonization of quality practices for nuclear medicine radioactivity measurements*" was started in 2004. Following the recommendations of the first meeting, a second consultants meeting was held and recommended to develop a set of procedures in the form of a draft Code of Practice in radioactivity measurement. Among other results of the CRP deployment, the elaboration of the above named document TRS454: *Quality Assurance for Radioactivity Measurement in Nuclear Medicine* was very important. The document presents in detail (Table 4, page 69) the types of tests and acceptance criteria for radionuclide activity calibrators to be performed upon the initial acceptance in the unit or after repair, daily checks in the hospital, monthly and annually. As for accuracy of measurement, an upper limit of 5% is imposed. In this respect, a radionuclide metrology laboratory is the entity providing assurance of metrological traceability chain directly, by providing standards, by performing calibrations and by organizing proficiency tests among the personnel doing measurements in radiopharmacy, in the control authorities, at the calibrators' producers and the nuclear medicine staff.The requirement of accuracy in the metrology laboratory is 2%. It can be primary activity standard, or a secondary one, metrologically traceable to a primary activity standard, disposing of a calibrated reentrant ionisation chamber, such as described by (Schrader, 1997).

(ii) Specific activity, expressed in units, Bq g^{-1} of solid mass. It defines the activity of the mass unit of the chemical element or solid compound and determines the capacity of

labeling, mainly for biomolecules, and also the radiopharmaceutical's toxicity for human body. Two situations must be taken into consideration:

- Obtaining of the radionuclide. If the radionuclide is obtained in the nuclear reactor by neutron activation, generally it contains a mass of inactive carrier, which is determined by spectrophotometry, or by calculation from irradiation data. The accuracy of these calculations rely on the precision of irradiation data: neutron flux Φ, activation section σ, irradiation time t, but also on the target data such as mass M, isotopic composition η, radionuclide half life, $T_{1/2}$. In the case of radionuclides obtained by irradiation at cyclotrone, or separated from a radionuclide generator, or when the radionuclide of interrest is different from the irradiated target, as for example ^{131}I obtained by irradiation of ^{130}Te, the obtained radionuclide is carrier free.
- Obtaining of the radiopharmaceutical product. In this case, the specific activity depends on the labeling yield, such as the labeling of various kits with ^{99m}Tc in the hospital, under the use of stanous chloride as catalist.

2.2.2 Physico-chemical parameters

(i) Radionuclidic purity, expressed as the ratio between the activity of the base radionuclide and total activity. This parameter is important from two points of view:

i. influence of impurities on accuracy of activity measurements and
ii. their contribution in the committed effective dose of the patient, mainly when the impurities have values of the *E/A* higher than the main radionuclide. One relevant example is the (^{99}Mo- ^{99m}Tc) generator, where $(E/A)_{Mo\text{-}99}$ =1.2 *mSv/MBq*, 55 times higher than for ^{99m}Tc; a 2% ^{99}Mo impurity will duplicate the committed effective dose. For this reason the ^{99}Mo impurity in ^{99m}Tc elute, known as "molybdenum breakthrough", is restricted at 0.1%. The precise determination of impurity level depends on the knowledge of the decay parameters, such as presented in the Monographie BIPM-5 (2004): half life, type and intensity of emitted radiations for all impurities and also on the precision of the method used in determination. In the simple case, when the involved radionuclides are gamma-ray emitters, the well-known gamma-ray spectrometry method, based on spectrometers provided with high resolution HPGe or Ge(Li) detectors, multichannel analyzers (MCA) and sets of software for processing of data, is used (Debertin & Helmer.1988). The energetic resolution is expressed in terms of full width at half maximum (FWHM) and reflects the ability of the system to distinguish two close energy full absorption peaks. Their calibration contains two components:

- The energy calibration is expressed in terms of number of energy units per MCA channel (generally keV/channel) allowing the identification of all radionuclides contained in a sample;
- The full absorption peak efficiency calibration consists in the determination of a calibration curve, generally expressed in terms of efficiency versus the logarithm of energy, used for the measurement of individual activities; it is established for a determined measurement geometry (distance detector – source) and for each type of measured recipient. The calibrations are performed by using sets of monoenergetic standard sources, covering the whole 50 keV – 3000 keV energy interval. The sets of standard sources are provided by a RML and are certified with uncertainties of (1- 5) %. The spectrometry systems are also provided with dedicated software sets,

allowing the determination of full absorption peak areas and for performing corrections for: geometry, matrix and sample volume, coincidence summation for multigamma emitting radionuclides. The determination of purity consists from the following steps: identification of the main radionuclide and of the impurities in the sample, according to the energy calibration; measurement of the areas of all full absorption peaks; calculation of individual activities, using the efficiency calibration curve and the gamma-ray emission intensity from the radionuclide decay scheme; calculation of the ratios between the activity of the main radionuclide and the sum (main radionuclide plus radio impurities). Generally, the impurity level is controlled only in the radiopharmacy, but in the case of molybdenum breakthrough, it must be controlled also in the hospital, due to the possible deterioration of molybdenum retention in the alumina column along its use. On this purpose, the radionuclide calibrators are usually provided with a lead shield, which absorbs the ^{99m} Tc, 140.5 keV gamma-rays. The detection of sole ^{99}Mo gamma-rays and use of ^{99}Mo calibration factor, corrected for the absorption of its gamma-radiations in the shield, allows the determination of the impurity level, expressed as the ratio between ^{99}Mo and ^{99m}Tc activities. The problem is more complex when pure beta or alpha-ray emitters are used. Some relevant examples:

a. Determination of ^{90}Sr content in ^{90}Y when a ^{90}(Sr+Y) generator is used. In this case, only liquid scintillation spectrometry (Grau Malonda et al. 1994) or counting is used (Wyngaardt. 2006).
b. Determination of alpha and beta impurities in ^{99m}Tc, due to fission ^{99}Mo used for generator production. In this case, the restrictive limits for alpha impurities are of the order of 10^{-9} and for beta emitters of the order of 10^{-6}. This level of impurities is possible to be measured only after the complete decay of the ^{99m} Tc elute by using the liquid scintillation counting, alpha/beta discrimination (Terlikowska et al. 2000).

(ii) Radiochemical purity or ratio between the activity of the main compound and sum of all chemical compounds. The determination is compulsory in the radiopharmacy, but it is advisable also in the hospital, when operations like the preparation of labeled kits is performed. For example, the determination of radiochemical purity of Labeled ^{99m}TcMDP, expressed as the ratio: ^{99m}TcMDP/(^{99m}TcMDP+Na$^{99m}TO_4$). This purity determination is important, as the tropism of the compound to the target organ/tissue is affected, resulting in the dangerous irradiation of other organs. The imposed limits are generally of 97-98%. The radiochemical purity is determined by using the radiochromatographic methods: either thin layer chromatography (TLC) or more sophisticated - high purity liquid chromatography (high pressure liquid chromatography)-HPLC. The determination consists of the measuring the activities of the two fractions and calculating the ratio between the activity of the main fraction and the sum of main and impurity fractions. The precision of measurement depends mainly on the linearity of the measurement instrument, which must be verified by using two standard sources with activity ratio of about 100, similar with the ratio of measured activities. The counting rates ratio must be equal with the ratio of sources activities, which must be certified with uncertainties <5%.

(iii) Chemical purity, defined by the existence of some nonradioactive elements. The chemical impurities can be: alumina, cooper, ions types $(NH_4)^+$ or $(NO_3)^-$ in ^{99m}Tc elutes from a generator. Their presence can produce the toxicity of the radiopharmaceutical, or can

deteriorate the labeling yield of the kits. They are usually determined in the radiopharmacy, but in some cases, the medicine units can dispose of the necessary equipment for control. The methods are specific to the analytical non radiation chemistry, such as spectrophotometry or colorimetry.

2.2.3 Biological and microbiological parameters

These parameters are of maximum importance mainly when the radiopharmaceutical is administrated as an injection, but they are beyond the scope of this chapter and will not be further presented.

3. Primary standard radionuclide metrology laboratory

From the content of section 2, one can conclude that the nuclear medicine applications of radionuclides raise many challenges to the nuclear physicists, from several points of view:

- A very long list of radionuclides is used for the production of radiopharmaceuticals. Other new radionuclides, presenting convenient physico-nuclear and chemical properties, are discovered and introduced in the radiopharmaceutical use.
- The quality requirements can only be accomplished by the very precise determination of the activity of radiopharmaceuticals and by a very deep knowledge of their physico-nuclear characteristics, generally defined as the decay scheme parameters. These two aspects are interconnected, each one depending strongly on the other.

The adequate solutions of these tasks are offered by the Radionuclide Metrology Laboratories, generally responsible national entities, which assure the continuity of the metrological traceability chain from the international level up to the nuclear medicine units.

General Metrology uses the basic terms which are defined according to the *International vocabulary of metrology – Basic and general concepts and associated terms (VIM), JCGM 200: 2008*:

Primary reference measurement procedure, Primary reference procedure = *Reference measurement procedure used to obtain a measurement result without relation to a measurement standard for a quantity of the same kind.*

Calibration = *Operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication.*

Measurement uncertainty = *Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.*

Metrological traceability = *Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.*

3.1 Activity measurement

The national metrology laboratories dispose of two modalities to assure traceability in activity measurement. In many cases, they are Secondary Standard Laboratories (SSL), transferring the activity unit, Becquerel, from the well know and internationally recognized primary standard laboratories, like NIST (USA), LNHB (France), NPL (UK), PTB (Germany), etc. Alternatively, a national primary standard laboratory, recognized at the international

level, by demonstrating the equivalence of its standards to the International System (SI), can solve entirely this task.
Figure 1 presents the equivalence and traceability chain to be established in activity measurement, from the International System (SI), assured by the International Bureau of Weights and Measures (Bureau International des Poids et Mesures-BIPM) through primary standard laboratories which disseminate the standards to the SSLs and end users, in our case the nuclear medicine units. In order to accomplish its duties, one primary laboratory has to solve the following tasks: it must set up the installations for absolute standardization of radionuclides, demonstrate its international equivalence and assure traceability to the lower levels.

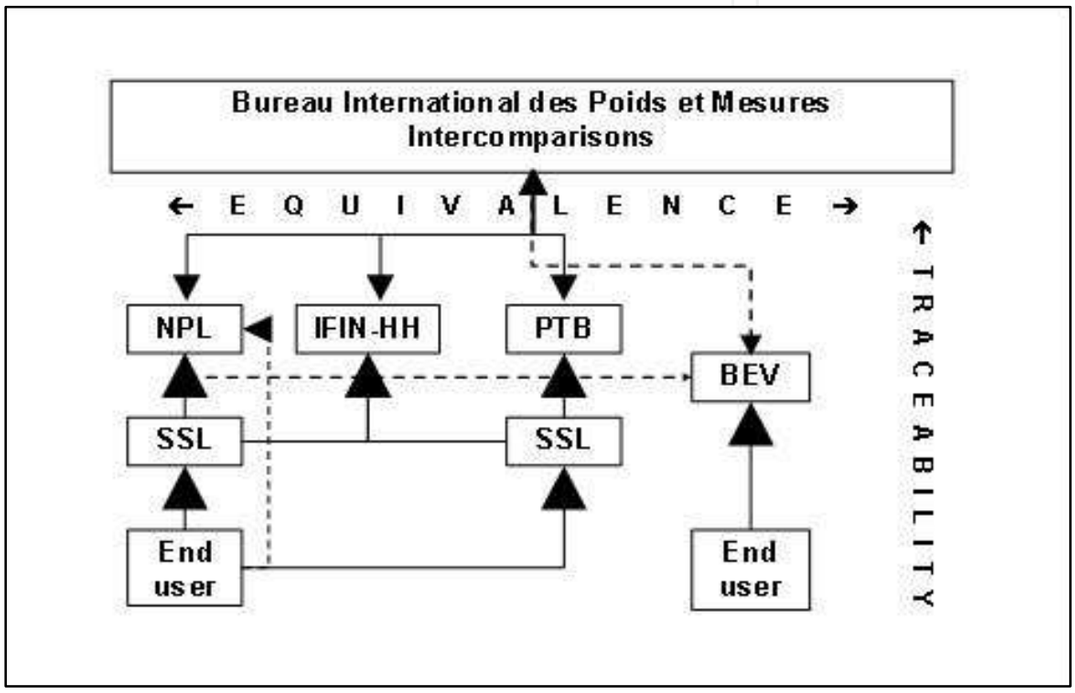

Fig. 1. Dissemination pathways for SI values of activity (From Woods & Sahagia. 2008).

3.1.1 Methods and installations for primary (absolute) standardization

The distinction between the radionuclide metrology and other metrology branches consists of the necessity to elaborate specific standardization methods almost for each radionuclide, due to the variability of decay schemes, and in the impossibility to construct an immuable standard, due to the radioactive dizintegration.
In radionuclide metrology, an absolute standardization is done by the following procedure: one detects the radiations emitted by a radioactive source and the method for establishing an adequate relation between the counting rate and the activity of the source is elaborated. A general relation is expressed as:

$$N_{rad} = \varepsilon\, s A = \varepsilon\, s N_0 \tag{1}$$

N_{rad} is the counting rate, s^{-1} (impulses per second) for the detected radiation; ε is the detection efficiency of the system; s, denoted also as (I, p) is the intensity of detected

radiations and *A*, or *(N_0)* is the activity of the source, Becquerel (*Bq*). Every standardization operation aims to determine as precisely as possible the quantity ε, or to find a method to eliminate it from relation (1)
Two basic methods are used, NCRP58 (1978). Methods based on the detection in a well-defined geometry (defined solid angle), the most used being the 4πsr geometry, applicable for radionuclides emitting a single type of radiations, and coincidence methods used for those emitting coincident radiations.

3.1.1.1 Methods based on determined geometry

Solid angle method is based on the precise calculation of the solid angle, of the absorption in air and in detector window, and of the radiations scattering correction. The method is used for the standarization of the alpha sources, in vacuum chambers, provided with Si barrier surface detectors; in other cases, for example beta radiations, it is not satisfactory precise.
Methods based on 4πsr geometry use a detection system assuring the quasi total detection of the radiations emitted by the source, which are used for measurement, what means that the following condition is fulfilled:

$$\varepsilon \approx 1 \tag{2}$$

The method of the 4π proportional counter, known as the method $4\pi PC$, is the most known. It is applicable to solid sources, or to radioactive solutions gravimetrically dropped on very thin solid supports, from pure beta emitters with high maximum energy, generally > 150 keV. The remaining corrections to be applied are due to: beta rays absorption in source mass (selfabsorption) and in its support. The method is frequently used for the standardization of the radioactive gases and is known as „gas fillig counter" (Stanga et al.2002). The corrections are due to the wall nondetection, mainly the extremity of counters. Another applied method is the sum peak counting, based on the use of a large NaI(Tl) well type crystal, with a thin window (Nedjadi et al.2007). It is used for radionuclides emitting gamma radiations with high energies and intensities, as for example: ^{124}Sb, ^{222}Rn decay chain, etc. The corrections are done by using Monte Carlo programs.
Liquid scintillator methods. The method is applicable to the radioactive solutions or gases, which are dissolved in a liquid scintillator. The detection geometry is 4πsr. The self-absorption and source support absorption are eliminated but other processes occur: the quenching and non-detection of low energy radiations. It is applicable to pure alpha emitters, for which $\varepsilon = 1$, and high energy pure beta emitters.

3.1.1.2 Coincidence methods

The methods are generally applicable for the radionuclides decaying with the emission of mixed radiations, such as: $\alpha - \gamma$; β - γ; x, $e_A - \gamma$. It is extended to the pure beta or electron capture radionuclides.
Coincidence method and installation $4\pi PC$-γ. A classical coincidence installation contains: a proportional counter (PC), one or two NaI(Tl) detectors and electronic modules, allowing the individual recording of the impulses provided by the two detection channels, and the coincidences recorded by a coincidence selector. The principle of the method is the following: the relations between the counting rates on the three channels: proportional counter – N_{PC}, gamma ray counting - N_γ, coincidence – N_c , the activity N_0 and the corresponding detection efficiencies ε_{PC} and ε_γ , are:

$$N_{PC} = \varepsilon_{PC} N_0; \quad N_\gamma = \varepsilon_\gamma N_0; \quad N_c = \varepsilon_{PC} \varepsilon_\gamma N_0 \tag{3}$$

Relations (3) are equivalent with:

$$N_{PC} N_\gamma / N_c = N_0 \tag{4}$$

Relation (4) shows that the efficiencies of the two detectors are eliminated and consequently the activity can be determined directly from the three counting rates. Relations (3) and (4) were written in very simplifying assumptions, which in reality can not be reached: the radiouclides have a simple decay scheme - an alpha or beta decay, followed by a gamma transition to the daughter ground level; the detectors are fully specialized; no perturbations due to the installation, such as background counting rate, dead times, resolution time of the coincidence circuit modifies the counting rates. The coincidence relations are more complex, and were written by (Gandy.1961) and (Baerg.1973). For decay scheme corrections the coincidence method is applied associated with an efficiency extrapolation variant, and for the instrumental corrections various formulae were deduced by (Grigorescu.1973) and (Smith.1978). Many specific methods were elaborated in the primary activity standard laboratories, among them being the Radionuclide Metrology Laboratory from the Horia Hulubei National Institute for Research & Development in Physics and Nuclear Engineering (IFIN-HH, RML) Bucharest, the Romanian owner of the primary activity standard. A coincidence installation was set up in the sixties and was continuously updated in this laboratory. The variant of the efficiency extrapolation, allowing to accomplish the decay scheme corrections, was developed and applied for many types of radionuclides. The classical extrapolation coincidence method was applied for the beta-gamma medical radionuclide ^{131}I, for which the whole traceability chain was established (Sahagia et al.2008a). The therapy radionuclides ^{153}Sm, ^{177}Lu and ^{186,188}Re, strong beta - weak gamma-ray emitters, have a "triangular" decay scheme and were standardized by a special extrapolation procedure (Sahagia et al.2005a,2005b,2002). For the radionuclide ^{99m}Tc, decaying by isomer transition in competition with internal conversion, a new type of coincidence scheme was applied, based on the coincidence between 119.5-138 keV conversion electrons and Tc *x*-rays (Sahagia.2006). Radionuclide ^{125}I is an electron capture gamma emitter; it was standardized by the *x - x, γ* coincidence method (Sahagia et al.2008b). The positron emitters, used for PET, PET/CT systems, like ^{68}(Ge + Ga) generator, or other radionuclides decaying by electron capture in competition with positron emission, were standardized by the positron-annihilation-ray coincidence, or combinations of radiations (Grigorescu et al.2004; Grigorescu et al.1996). In the present time, in many laboratories, the classical, analog, coincidence set up is replaced by the Digital Coincidence Counting (DCC) (Buckman et al.1998). At the same time, instead of the PC, a liquid scintillation counter (LSC), associated with a NaI(Tl) detector is used for coincidence measurement (Chylinski & Radoszewski.1996)

Efficiency tracer method is an extension of the coincidence method applied for the standardization of pure beta decaying radionuclides. The solution to be standardized is mixed with a standard solution from a beta-gamma emitting radionuclide, preferable with a simple decay scheme, with a beta spectrum close to that of the radionuclide to standardize and chemically compatible with it. For the two radionuclide's mixture, relation (3) becomes:

$$N_{PC} = \varepsilon_{PC1} N_{01} + \varepsilon_{PC2} N_{02}; \quad N_\gamma = \varepsilon_\gamma N_{01}; \quad N_c = \varepsilon_{PC} \varepsilon_\gamma N_{01} \tag{5}$$

Index *1* refers to the tracer and *2* to the pure beta emitter. By an extrapolation procedure, a relation is established between the two ε_{PC1} and ε_{PC2} efficiencies, allowind the calculation of

activity N_{02} of the pure beta radionuclide.The method is applied for therapeutic pure beta radionuclides, like ^{89}Sr, or other important radionuclides as ^{137}Cs (Razdolescu et al.2002a, Sahagia.1981) ^{32}P, ^{90}Y.

3.1.1.3 Advanced methods based on the liquid scintillation counting

The method consists of mixing the radioactive solution with a liquid scintillator (LS). The energy of the radiations is transferred to the LS; it emits light photons, which produce photoelectrons, multiplied in a photomultiplier (PMT). Electron impulses are collected at the PMT anode. The detection efficiency is superior to that of proportional counters, but it depends strongly on the radiations energy. A calculation model, known as the „Free parameter principle" was developed, leaving from the idea that the sum of fenomena: luminous photons emission in LS, their arrival at PMT photocathode and emission of a photoelectron as result of interaction, is described by a Poisson distribution law. Another influence of LS is the quenching; it can be due to its chemistry, but the most important is the ionization quenching, $Q(E)$, which is described by an empirical relation, written by (Birks.1964). Taking into account all these fenomena, a relation connecting the detection efficiency, ε, equal to the probability of producing a photoelectron, $P(\lambda,E)$, with the counter parameters and ionizing radiation energy, E was deduced. (Broda et al.2007; Pochwalski&Radoszewski.1979):

$$\varepsilon = P(\lambda, E) = 1 - e^{-\frac{EQ(E)}{\lambda R}} \tag{6}$$

λ is called the free parameter and R is the number of photomultipliers in the system. In relation (6) it is important to adjust the free parameter such as to reflect the measurement conditions. On this purpose, two main models were developed.

CIEMAT/NIST method consists of the use of a LS counter provided with two PMTs in coincidence, in order to diminish the influence of background; commercial counters can be used. The adjustment of the free parameter is achieved by using an efficiency tracer, consisting of a tritium standard solution. The model contains several steps: a relation is established between the tritium detection efficiency and a quantity equivalent of the free parameter, known as quenching indicator parameter (QIP) (Grau Malonda.1999), measured by using the Compon radiation of an external source; a theoretical relation is calculated between the efficiency of tritium and that of the nuclide to standardize, for different QIP values, based on the beta spectra characteristics. Using a determined QIP value, one calculates the nuclide efficiency from the theoretical efficiency relation, corresponding to that QIP.

Triple to double coincidence ratio (TDCR) method makes use of a special counter, provided with three PMTs, connected in double and triple coincidences. Leaving from the general equation (6), the efficiencies, equal to the probabilities of registration for the logical sum of double, ε_d , and respectively triple, ε_t , coincidences were written by (Broda et al.2007; Pochwalski&Radoszewski.1979):

$$\begin{aligned} \varepsilon_d &= d(E) = 3\left(1 - e^{-\frac{EQ(E)}{3\lambda}}\right)^2 - 2\left(1 - e^{-\frac{EQ(E)}{3\lambda}}\right)^3 \\ \varepsilon_t &= t(E) = \left(1 - e^{-\frac{EQ(E)}{3\lambda}}\right)^3 \end{aligned} \tag{7}$$

These relations are calculated theoretically, from the radionuclide spectrum, by itteration for a big number of values of the free parameter λ, by using computer programs, like SPEBETA; TDRCB-1, 2, 7; DETECSZ, etc., elaborated at LNHB-France and RC Poland. On the other hand, an experimental ratio between the counting rates of the two types of coincidences, equal to the efficiencies' ratio, is determined. They depend on the activity N_0 and efficiencies, as:

$$R_D = N_0 \varepsilon_d \; ; \; R_T = N_0 \varepsilon_t \tag{8}$$

The theoretical ratio of efficiencies, corresponding to the adjusted free parameter is the optimum, when:

$$\frac{\varepsilon_d}{\varepsilon_t} = \frac{R_D}{R_T} \tag{9}$$

In this manner, the efficiencies are determined, and the activity N_0 is calculated from relations (8)

A TDCR system was set up in IFIN-HH,RML, with the assistance of Dr. Philippe Cassette from LNHB. It was used for the standardization of radionuclides as ^{3}H, ^{89}Sr, ^{63}Ni and was validated by international comparisons (Razdolescu et al.2004; 2006). Recently, a new counter was set up in RML, replacing the three PMTs with 6 channel photomultipliers (CPM) and designing a new optical chamber (Ivan et al.2010). It has the advantage of being compact and portable.

3.2 Validation of the primary installations and methods; international equivalence

3.2.1 The International System

The International Committee for Weights and Measures (CIPM) coordinates the metrology branches through the Consultative Committees, as the Comité Consultatif des Rayonnements Ionisants – CCRI. CCRI is divided in three sections. The Section II, CCRI(II) - Measurement of Radionuclides, coordinates the Radionuclide Metrology. The Bureau International des Poids et Mesures-BIPM, Sèvres, http://www.bipm.org France, has the custody of the international standards. The equivalence of the primary standards is assured at this level by absolute methods of standardization. At the regional level, the Regional Metrology Organizations (MRO) are operational. In Europe there exist: EURAMET - European Association of National Metrology Institutes and COOMET - Euro-Asian Cooperation of National Metrology Institutes. The connection between BIPM and MROs is assured by the Joint Committee of the Regional Metrology Organizations and the BIPM - JCRB. At this level one assures the traceability also by using secondary (relative) standardization methods. The CIPM-MRA, Mutual Recognition Arrangement (1999), defines the recognition of the calibration and measurement certificates issued by the National Metrology Institutes. For example, Romania is part of CIPM-MRA. The document contains four annexes: Annex A - List of signatories; the Romanian signatory is the Romanian Bureau of Legal Metrology - National Institute of Metrology (BRML-INM); Annex B - Key Comparison Data Base (KCDB) per Institute; Annex C- Calibration and Measurement Capabilities (CMC); Annex D - Key Comparison Data Base. The condition for the applicability of CIPM-MRA by the signatory countries is the demonstration of the equivalence of the primary standards, or of the traceability for the others, such as presented

in figure 1. The equivalence is demonstrated only by the participation at international comparisons. IFIN-HH, RML, has participated at international comparisons since 1962. *The Key Comparison Data Base (KCDB) Annex B of the CIPM – MRA*, can be found at the address: http://kcdb.bipm.org/AppendixB/KCDB_ApB_search.asp. The participants in CIPM-MRA are the National Institutes of Metrology (NMIs), but for specialized metrology branches as the ionizing radiations, the participants can be the Designated Institutes. In Romania, according to the protocol concluded between BRML-INM and IFIN-HH it is established that IFIN-HH is designed as the owner of the primary activity (Becquerel) and derived quantities standard, with national and international responsibilities in the field:

- Designed Institute as responsible for participation in the CIPM-MRA, included in *Annex A of the CIPM-MRA, List of signatories.*
- Associated Institute to EURAMET, responsible for the Technical Committee of Ionizing Radiations, TC-IR

Due to its scientific authority, IFIN-HH became also: Member of the International Committee for Radionuclide Metrology (ICRM) in 1980 and Member of the Consultative Committee Section II, CCRI(II), in 2004

3.2.2 Validation of methods and establishment of equivalence by key comparisons

Definition of the Key Comparisons, according to VIM*: Selected comparisons taken formally into account for the establishment of equivalence.* CCRI(II) may approve also supplementary comparisons, initiated by other organizations, to be used for establishment of equivalence: EURAMET, COOMET, IAEA, JRC-IRMM, etc. Relative methods may be used at this level, in order to extend the applicability of the CIPM-MRA, Annex C.

The Comparisons are of the categories:

- *Comparisons type « CCRI(II)-K2. Radionuclide (Ex. Am-241)"*. They are organized at worldwide scale. A single batch of radioactive solution is used for the preparation of all the samples which are sent to the participants, who measure and send to the BIPM the filled-in Reporting Form, containing the results. The reports are evaluated at BIPM and the Draft reports are drawn up. The Draft B is submitted to the approval of the CCRI(II) and published. For example, IFIN-HH, RML is registered with such comparisons in the KCDB with the radionuclides: ^{241}Am, ^{109}Cd, ^{139}Ce, ^{134}Cs, ^{137}Cs, ^{152}Eu, ^{55}Fe, ^{3}H, ^{125}I (2), ^{192}Ir, ^{177}Lu, ^{54}Mn, ^{32}P, ^{75}Se, ^{89}Sr, ^{204}Tl, ^{65}Zn.
- *Comparisons: "BIPM.RI (II)-K1.Radionuclide"*. BIPM disposes of two reentrant (well type) ionization chambers, CENTRONIC IG11/20A, as the basis for creation of the International Reference System - SIR, for gamma-ray emitters (Ratel. 2007). The key comparison is carried out by the individual preparation and certification of an ampoule with standard solution by the participant laboratory, which is then sent to the BIPM with the Comparison filled-in Form. It is re measured at BIPM and the two results are compared. IFIN-HH, RML is registered with the radionuclides: ^{110m}Ag; ^{133}Ba; ^{60}Co (1983 and 2007); ^{134}Cs; ^{131}I; ^{57}Co; ^{137}Cs
- Supplementary Comparisons

Type: "EURAMET.RI(II)-S5.Radionuclide". These comparisons are deployed as Decay Data Evaluation Projects-DDEP. The first step of comparisons is similar to the CCRI(II)-K2. The second step consists of the measurement of the emission intensities for *x* and gamma-rays. IFIN-HH, RML is registered with: ^{169}Yb; ^{65}Zn; ^{124}Sb.

"IAEA-CCRI(II). Matrix content. Radionuclides". These comparisons are organized within the frame of the International Atomic Energy Agency (IAEA) - Coordinated Research Projects

(CRPs) and are approved by the CCRI(II); they refer to special types of samples and relative methods are accepted. IFIN-HH, RML is registered as "*CCRI(II)-S6.Radionuclide*", for the radionuclides ^{57}Co and ^{131}I, of interest in nuclear medicine.

Establishment of the SI Activity Unit (Becquerel) by key comparisons.

The Activity Unit is established individually for each radionuclide, after the evaluation of the key comparison result, which is expressed as the Key Comparison Reference Value – KCRV.
Four methods are used to calculate the KCRV (Ratel.2007): arithmetic and weighted mean, median and weighted median. The most adequate variant is selected; in most cases, the arithmetic mean is preferred. The outliers are established after applying the exclusion criteria. The KCRV and its uncertainty are approved by the CCRI(II) and may be modified in time, after accumulating new results for the respective radionuclide. The "outliers" are not eliminated from KCDB, but their difference from KCRV must be taken into account when reporting the calibration uncertainties.
When both the *SIR-BIPM.RI(II)-K1.Radionuclide* and the *CCRI(II)-K2. Radionuclide* comparison results are registered for the gamma-ray emitters, a link is established between the two types of comparisons, through the measurement in the BIPM ionization chamber of the ampoules sent for the *K2* comparison.
Equivalence. An equivalence matrix is calculated. Two main quantities are reported and compared: Difference between the individual result and KCRV, (D_i) and its uncertainty (U_i), for a coverage interval k =2. The ratio of these quantities is the measure of degree of equivalence. The CCRI(II) approved "Draft B" is published in the KCDB and in *Metrologia, Technical Supplement issues*. IFIN-HH, RML, is registered in KCDB with 28 radionuclides.
Equivalence validity. A validity interval was adopted by consensus. Consequently, in order to maintain the equivalence for some radionuclides, IFIN-HH repeated the comparison. It participated in 1983 and in 2007 at the *SIR-BIPM.RI(II)-K1*.Co-60 comparisons. As for ^{134}Cs, the participations were: *CCRI(II)-K2* in 1978 and *SIR-BIPM.RI(II)-K1* in 2006 and for ^{137}Cs, the participations were: *CCRI(II)-K2* in 1982 and *SIR-BIPM.RI(II)-K1* in 2009.
Example: *Analysis of the IFIN-HH, RML result at the medical ^{131}I key comparison SIR-BIPM.RI(II)-K.1.I-131, 2007* (Ratel et al.2008). *KCRV* = (40400 ±40) *MBq*; *IFIN-HH* value = (40371 ± 139) *MBq*; *D*i =0.07%; *U*i=0.65% . Consequently, the IFIN-HH, RML's result was taken into account in the calculation of the *KCRV*.

SI Activity Unit (Becquerel) for other radionuclides.

A matrix of radionuclides, codified by colors, according to the standardization difficulty by method, was established by the CIPM-CCRI(II) Key Comparison Working Group (KCWG), within the document Grouping Criteria Radionuclides for Supporting CMCs (Karam.2007). It can be used as follows. A red coded radionuclide measured by LSC, such as ^{3}H, supports ^{89}Sr, ^{90}Y, LSC measured, and green color coded.

3.3 Implementation and recognition of the Quality Management System – Approval of CMC files

An international agreement for the practical use of the results obtained by the National Metrology Institutes (NMI) in assurance of the traceability chain and recognition of the measurements and certificates was concluded through the document: "*Joint statement by the CIPM and ILAC on the roles and responsibilities of national metrology institutes and national recognized accreditation bodies*". At the level of EURAMET, the implementation of the Quality

Management System (QMS) is monitored by the EURAMET, Technical Committee – Quality, TC-Q.

At the level of CIPM - MRA, the statement is practically applied by the use of the Annex C of the CIPM-MRA, Calibration and Measurement Capability files – CMCs. The approval and publication of CMCs for a NMI is the result of two types of evaluation components for the international recognition: (i) Approval of the international equivalence for primary and of the traceability for secondary standards; (ii) Implementation of the QMS and recognition by the MRO's, TC-Q.

i. *Approval of equivalence and traceability.* The NMI, member of one MRO, draws up the primary or secondary CMC files. The statement is compared with the KCDB for primary, or in our case EURAMET for secondary standards. After the inter MROs' peer review process, they are submitted for the approval of the JCRB.
ii. *Implementation and approval of the QMS.* The EN/ISO/IEC 17025:2005, referential "*General requirements for the competence of testing and calibration laboratories*" is applied. A complete documentation and its implementation are presented at the annual meetings of the EURAMET, TC-Q. The technical experts monitor the documents and after the first approval, the QMS is annually reconfirmed. This is a prerequisite condition to maintain the CMCs in the published in Annex C of MRA. *Example, IFIN-HH, RML situation.* 34 CMC files, Radioactivity standards, passed the peer review process; the QMS was approved in 2007 and annually reviewed. All CMCs were approved by the JCRB in April 2008 and published in CIPM-MRA, Annex C. http://kcdb.bipm.org/AppendixC/default.asp

4. Setting up of the activity secondary standard systems

Realisation of the activity secondary standards.

Such as presented in figure 1 and as pointed in the references TRS 454 (2006) and (Zimmerman & Judge. 2007), the practical realization of the metrological traceability chain is possible by using the activity secondary standards. They are transfer instruments of the activity unit from the primary to the lower order, working standards, for the end users, through standard (reference) products or calibration services. They consist of installations for the secondary (relative) standardization; their calibration is done with sources and solutions absolutely standardized with the primary standards. In the case of the primary laboratories they use their own primary standards. In the case of the secondary standard laboratories (SSL), the standards leave from another primary laboratory, the traceability route being declared. The practical work at IFIN-HH, RML was described in (Sahagia & Woods.2008).

4.1 Secondary standards for high activity radiopharmaceutical solutions

The secondary standard for high activity solutions is a reentrant (well type) ionization chamber, filled with an inert gas as nitrogen or argon, at high pressure, of a special construction, largely described by H. Schrader in Monographie BIPM-4 (1997), or a commercial radionuclide calibrator. It is calibrated with standard solutions absolutely standardized, from the radionuclides of interest. The ionization current, registered by the associated electrometric circuit, is due to the radiations entering in the sensitive volume of the chamber and ionizing the filling gas. This chamber is mainly used for the measurement

of activity for gamma-ray, but also for strong beta-ray emitters, when the ionization current is produced by the bremsstrahlung radiations. Usually, the calibration factor is expressed in terms of absolute or relative efficiency, or in ionization current per activity unit, $pA\ MBq^{-1}$. The calibration must be performed for several geometries of the recipients containing radioactive solution, or gelatin capsules in the case of iodine radioisotopes, as the calibration factor depends on the geometrical dimensions. For example, the IFIN-HH, RML well type ionization chamber is of the type CENTRONIC IG12/20A, filled with argon at a pressure of 2MPa (20Atm); its construction was first described in (Grigorescu et al. 2003). Recently, the old electrometric system was replaced with an electrometer Keithley E6517A. The validation of the calibration factors was done by several comparisons: (i) with the measurements performed at PTB-Braunschweig-Germany with PTB standard solutions; (ii) with the IFIN-HH, RML results obtained in international comparisons; (iii) respectively with the value of the KCRV (Sahagia et al. 2010). The calibration factors are determined for the radionuclides: ^{241}Am, ^{57}Co, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{153}Sm, ^{177}Lu, ^{75}Se, ^{169}Yb, ^{131}I, ^{133}Ba, ^{51}Cr, ^{192}Ir, ^{134}Cs, ^{137}Cs, ^{54}Mn, ^{65}Zn, ^{60}Co, ^{152}Eu and for three geometries: (i) Solid sources; (ii) ^{131}I gelatin capsules; (iii) Solutions of volumes: 2 mL (PTB), 3.6 mL (SIR-BIPM), 5 mL (P6 used for radiopharmaceuticals). From the above list one may notice that the calibration is assured for the majority of medical radionuclides. The determined calibration factors allow the measurement and certification of the radiopharmaceutical solutions or capsules to be used for: (a) the calibration of the radionuclide calibrators, including those belonging to the radiopharmaceutical unit from IFIN-HH, (b) to be distributed to the interested laboratories, or (c) to be used for organization of national comparisons. The chamber operation is in compliance with the QMS rules, established in agreement with the requirements of the EN ISO/IEC 17025:2005 and TRS 454 document. The calibration uncertainty is in all cased less than 2.0%.

4.2 High resolution spectrometric system

In the field of nuclear medicine, spectrometric systems are used for the measurement of the radionuclide impurity level in radiopharmaceuticals (RPMs); in order to perform an adequate check of the requirements imposed to the RPMs, the system must have a high resolution, to allow the identification of the main radionuclide and impurities, and to be sensitive enough (to have a low background) in order to detect impurities content of the order of <0.1%, such as it is required for ^{99}Mo content in ^{99m}Tc.

IFIN-HH, RML disposes of a system containing a high resolution HPGe detector: relative efficiency 29%; energy interval 35 *keV* – 3 *MeV*; resolution: 0.85 *keV* (122 *keV*) and 1.74 *keV* (1.332 *MeV*) and a computer driven, software GAMMA VISION, V 6.01 spectrometric analyser. The specialized program GESPECOR (Sima & Arnold. 2002), for geometry, matrix and coincidence summation corrections is implemented. An efficient shield, consisting from: 10 cm old lead; 1 *mm* tin; 2 *mm* electrolytic cooper, assures a maximum integral background rate on the whole energy interval of 1.4 s^{-1}. The system is calibrated in terms of energy and efficiency with standard sources, in various geometries from point sources up to volume recipients, prepared from standard solution absolutely standardized, by the coincidence method. Various distances, from zero, up to 44.3 *cm* from the detector surface are used in measurements, depending on the activity interval. The calibration of the system was also validated by the participation at international NPL-UK or IAEA exercises for the measurement of various volume samples, containing mixtures of radionuclides (Luca et al. 2010). The system is taken as reference for the dedicated HPGe spectrometer used in the radiopharmacy unit.

Another use of the IFIN-HH, RML's spectrometric system is the precise determination of the emission intensity of gamma-rays for radionuclides of medical use. These parameters are of maximum importance for activity standardization by primary methods, as in most of measurements they are basic parameters in activity calculation. On the other hand, the efficiency and safety of the medical procedure depends directly on their precise knowledge. The precise value of half life is directly used in nuclear medicine units for the calculation of activity at the moment of administration. The calculation of patients' doses is based on the values of: activity, half life, radiations - types, energies and emission intensities. On the international scale, projects of the type*: "EURAMET.RI(II)-S5.Radionuclide"* are organized, for the experimental determination of emission intensities and evaluation projects coordinated by the Decay Data Evaluation Program (DDEP) are deployed. IFIN-HH, RML participates in both types of programs. For example, recently the laboratory participated at the exercise, organized for the new PET radionuclide ^{64}Cu, EURAMET project 1085 (Bé et al. 2011). RML standardized absolutely solutions from ^{64}Cu and ^{68}Ga by the coincidence method (Sahagia et al. 2011). Point solid sources from standard solution were prepared gravimetrically, and were used for the determination of their decay parameters: gamma-rays emission intensities with the calibrated HPGe spectrometric system and half life by the use of the CENTRONIC IG12/20A ionization chamber (Luca et al.2011).

5. The Radionuclide Metrology Laboratory support to the nuclear medicine

A primary/secondary standard laboratory is the entity which can assure the continuity of the metrological traceability in the measurement and characterization of radiopharmaceuticals in radiopharmacy units, national control authorities and hospitals from the top level, SI, up to the end user, the patient, by the following standards delivery and calibration operations (Zimmerman et al. 2007):

- Radioactive standards to be used in the interested entities;
- Calibration or Metrological Check of the Radionuclide Calibrators;
- Organization of national comparisons and proficiency tests.

These activities need to be accomplished under the regime of national accreditation, as a Calibration and Testing Laboratory, according to the provisions of the standard EN ISO/IEC 17025:2005 *"General requirements for the competence of testing and calibration laboratories"*. For example IFIN-HH, RML obtained the accreditation for both types of activities, from the Romanian accreditation body, RENAR, member of the European Accreditation (EA), for the products and services for clients, after implementing a Quality Management System (QMS). The QMS consists of the documentation and practical realization of the documents' provisions. The main documents, covering the Chapters 4 and 5 of the EN ISO/IEC 17025:2005 standard, are: RML Manual-containing the basic statement of the QMS, an Organizational procedure and two sets of procedures: System (Management) procedures (MP) and Work procedures (WP) and instructions (WI). The accreditation was obtained in 2009, for a 4-year period; annual survey audits of RENAR representatives are done. In contrast with other calibration or testing laboratories, where the accreditation refers to some well-defined activities, in our quality of primary standard laboratory, we have first of all the responsibility for the quality of primary, absolute standardizations, on the top of traceability chain, not in direct connection with customers' requirements. The first consequences are: (i) The traceability chain must be well defined and demonstrated in the laboratory. (ii) An internationally recognized expert must conduct the technical evaluation

of the laboratory. On the other hand, as a national provider of radioactive standards, the RML must meet quality requirements in their production.

(i) *Definition of Activities and Establishment of Traceability Chain.* Clear distinction of the two types of activities in relation with the RENAR accreditation was defined: Calibration activities and Testing activities. (a) The calibration branch required a sharp definition of the traceability chain and activities deployed in regime of quality management. The declared activities under accreditation are: (I) Attestation of the installations for the absolute (direct) standardization, mainly used for international comparisons, in order to prove the international equivalence of the Romanian standards, and for the preparation of standard sources and solutions used for the calibration of the secondary equipment. (II) Calibration and metrological check of the secondary installations for the relative (indirect) standardization. (III) Standardization of the radioactive standard sources and solutions. (IV) Preparation and relative or absolute standardization of radioactive sources and solutions, under the quality management system. The traceability chain continues outside the laboratory, in connection with the users, and implies: (V) The delivery of radioactive sources, with Calibration Certificates, under the quality management system. (VI) The calibration and metrological check of activity measurement installations. (VII) The organization of inter laboratory comparisons (ILCs) and proficiency tests (PTs) for the testing and calibration laboratories. (b) The testing branch of accredited activities refers at the Analysis of very low activity samples by the gamma-ray spectrometry. Another special aspect in the application of the requirements of the 17025:2005 Standard in our case is the responsibility of the National Nuclear Authority (CNCAN) regarding the radioprotection of the workers, public and patients. In this respect IFIN-HH, RML was CNCAN designed also as a notified calibration and testing laboratory for the nuclear field.

5.1 Radioactive standards for nuclear medicine

The calibration and metrological check of the equipment for measurement of the radioactivity imposed the development of technics for the preparation of a large variety of standard sources and solutions, to be used in-house, or delivered to the external customers which are performing radioactivity measurement. A general WP, coded AC-PL-LMR-10, describes the common operations and detailed WIs present the specific operations.

Radioactive Solutions. A large variety of radioactive solutions, physico-chemically stable, adequate as radioactivity standards, are prepared (Grigorescu et al.1975). Some of them, even for external users' delivery, are standardized absolutely, or alternatively, by the use of the calibrated ionization chamber. They are certified in terms of radioactive concentration, *Bq* g^{-1}, and in total activity, *Bq,* per recipient, flame or mechanically sealed in glass ampoules or P6 vials.

Point and Large Area Alpha and Beta Sources. These sources are of immediate interest, both for calibration of contamination monitors (contaminometers), as well as for the effective measurement of the so called "Gross Alpha" and "Gross Beta" radioactive content of environmental, industrial and food chain samples. Their preparation and measurement of the particle emission rate in a 2πsr geometry are described in (Sahagia et al. 1996a).

5.2 Calibration and metrological check of measurement equipment

The main requirements regarding the characteristics of the equipment for the measurement of activity and of the physico-chemical parameters were described in section 2. In order to satisfy them, a radionuclide metrology laboratory is asked to perform calibrations or other

metrology checks over it. The radionuclide calibrators are the most used devices for the measurement of activity in radiopharmacy, control units and hospitals (Razdolescu et al.2002b). In some cases the National Metrology legislation imposes their metrological control, according to legal metrology norms, and in others it is required their calibration at defined time intervals, by a metrology laboratory, accredited for calibration. In our case, the legal metrological control was mandatory until 2009. Starting with 2010, the calibration-recalibration was preferred. In this respect, IFIN-HH, RML obtained the RENAR accreditation for these operations within its QMS. The WP codified as AC-PL-LMR-11 is applied. As a general remark from our calibration experience is that the Romanian hospitals staff increased in time its awareness regarding the quality of activity measurement and more and more nuclear medicine units benefit from our laboratory's services of calibration, at present time regarding the radionuclides: ^{99m}Tc and ^{131}I. The deviations of the calibration factors from the reference values are generally within ±5%. The IFIN-HH radiopharmacy is under the permanent metrological survey of the RML. As this unit has under study new radiopharmaceuticals, the laboratory was asked to assess calibration factors to the radionuclide calibrators for the new radiouclides: ^{186}Re, ^{188}Re, ^{153}Sm, ^{177}Lu.

The second important action is the calibration of the HPGe spectrometric system used in the radiopharmacy for the control of radionuclidic impurities. It is calibrated and regularly recalibrated in energy and efficiency by the representatives of RML, using standard solutions prepared in RML, under accreditation regime, and the calibration procedure WP code AC-PL-LMR-0100 is applied.

Other equipment, belonging the radiopharmacy unit, are the radiochromatographs used in the control of the radiochemical purity; for their calibration and linearity check, a set of solid point standard gamma-ray emitting sources are used; for the case of ^{131}I control, two ^{133}Ba standard sources are measured. The action is also under accreditation regime and the WP code AC-PL-LMR-12 is applied.

Each nuclear medicine unit, operating with open radioactive sources, is provided with contaminometers for the control of radioactive contamination of surfaces, devices, clothes, operator hands, etc., which can occur during the medical procedures. This equipment can be under the legal metrological control of the state as it is in Romania, or only is recalibrated at defined intervals. The Romanian secondary standard laboratories performing these checks use large area standard sources emitting beta radiations, in most cases ^{90}(Sr+Y) sources. IFIN-HH, RML is the provider of these standard sources and also performs their calibration (Sahagia et al. 1996b).

5.3 Organization of national comparisons and proficiency tests

The most significant test, recognized as relevant in the evaluation of the capability of a laboratory performing measurements, is the participation in proficiency tests. For example, even when the calibration factors of the radionuclide calibrators are correct, the measurement in a hospital implies also the skill of the operating staff. Non experienced people are possible to choose wrong calibration factors' values, to do wrong readings and activity calculation on the administration time. From our practical experience, one may conclude that the proportion of laboratories with unsatisfactory results in proficiency tests is higher than that of wrong calibrated equipment. This is the reason for which in some countries the participation in proficiency tests is mandatory, but in others like Romania, it is only voluntary. IFIN-HH, RML organized in the past several national comparisons mainly

for a scientific output, in order to understand which explanations for noncorresponding results are. The comparisons regarded the measurement of ^{131}I (Sahagia et al.1996b) and the set ^{99m}Tc and ^{57}Co, (Sahagia & Woods. 2008c). Within the frame of the above cited *IAEA, CRP E2.10.05*, a series of international actions were deployed, in order to harmonize the measurements in the participant countries, all over the world. The actions were organized in two steps. The first step was the participation of the national reference laboratories (primary or secondary) in two comparisons organized by the IAEA, recognized also as supplementary CCRI(II) –S6 comparisons, on ^{131}I and ^{57}Co (used a as mock solution for ^{99m}Tc), intended to verify their calibration capability. The results were presented by the comparisons organizers in the papers (Zimmerman et al. 2008; Zimmerman & Palm. 2010). After the evaluation of the results, each national laboratory organized then two national comparisons, for the radionuclides ^{131}I and ^{99m}Tc. IFIN-HH, RML organized the comparisons according to the prescriptions of the WP code AC-PL-LMR-07, written in accordance with the international documents: ISO Guide 43 *„Proficiency testing by interlaboratory comparisons"* Part 1: *„Development and operation of proficiency testing schemes*" and Part 2: *„Selection and use of proficiency testing schemes by laboratory accreditation bodies"* and following also the recommendations from the *Protocols on the organization of national comparisons of radiopharmaceuticals*, established within the frame of the *IAEA CRP. E2.10.05*.The analysis of the results was reported in the papers (Sahagia et al. 2009; Sahagia et al. 2010b). As conclusions from these tests are the proportions of hospitals measuring satisfactory the activities of the two radionuclides. In the case of ^{131}I, from a total number of 15 reported values, a number of 11 results are within the difference limit from reference value <5%, and 12 results within the limit <10%, a proportion of 80% from participating units, being in compliance with the Pharmacopoeia; for ^{99m}Tc, from 7 reported values, a number of 5 results are within < 5 % difference from the reference value, and 7 results within the limit < 10 %, a proportion of 100% from participating units. Regarding ^{131}I comparisons, after finalizing the *IAEA CRP. E2.10.05*, an interesting paper, summarizing all 8 national laboratories comparisons' organization and results was published recently (Olsovcova et al. 2010); a similar paper is in preparation, for presentation of the ^{99m}Tc national comparisons.

6. Conclusions

- Nuclear medicine benefits from a very wide range of radionuclides, to be used as radiopharmaceuticals for diagnosis and therapy procedures.
- The radiopharmaceuticals are classified as high pharmaceutical risk products, and therefore they must be very carefully characterized in terms of the main parameters: metrological, physico-chemical, biological.
- The precise measurement of activity is of crucial interest, as it determines directly the committed effective dose of the patient in diagnostic and organ/tissue absorbed dose in therapy.
- Precise measurements of activity are also implied indirectly in the full characterization of the radiopharmaceuticals' parameters.
- The Radionuclide Metrology Laboratory can assure the metrological traceability chain for activity starting from the primary level, by demonstrating its international equivalence, or starting from the secondary one, the traceability route being necessary to be declared.

- The Radionuclide Metrology Laboratory can offer the necessary support to the nuclear medicine for the safe and efficient use of radiopharmaceuticals, by assuring the standards and the metrology services to the implied entities: radiopharmacy, control laboratories, equipment producers, nuclear medicine units.

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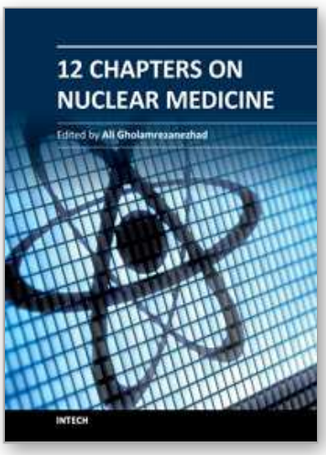

12 Chapters on Nuclear Medicine

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The development of nuclear medicine as a medical specialty has resulted in the large-scale application of its effective imaging methods in everyday practice as a primary method of diagnosis. The introduction of positron-emitting tracers (PET) has represented another fundamental leap forward in the ability of nuclear medicine to exert a profound impact on patient management, while the ability to produce radioisotopes of different elements initiated a variety of tracer studies in biology and medicine, facilitating enhanced interactions of nuclear medicine specialists and specialists in other disciplines. At present, nuclear medicine is an essential part of diagnosis of many diseases, particularly in cardiologic, nephrologic and oncologic applications and it is well-established in its therapeutic approaches, notably in the treatment of thyroid cancers. Data from official sources of different countries confirm that more than 10-15 percent of expenditures on clinical imaging studies are spent on nuclear medicine procedures.

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